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CLINICAL THERAPEUTICS

Ampicillin and Ceftriaxone Solution Stability at Different Temperatures in Outpatient Parenteral Antimicrobial Therapy

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ABSTRACT The inclusion of ampicillin-containing regimens in outpatient parenteral antimicrobial therapy programs (OPAT) depends upon solution stability under conditions similar to those experienced in these programs. Lack of this information could hinder the inclusion in OPAT of patients suffering from *Enterococcus faecalis* infective endocarditis treated with ampicillin plus ceftriaxone. The purpose of this study is to determine the stability of ampicillin and ampicillin plus ceftriaxone solutions in a simulated outpatient setting conditions. Solutions of ampicillin 24 g/liter and ampicillin 24 g/liter combined with ceftriaxone 8 g/liter were stored at 25°C ± 2°C, 30°C ± 2°C and 37°C ± 2°C for 48 h. Chemical and physical stability were evaluated at 20, 24, 30, and 48 h after manufacturing. The solutions were considered stable if the percentage of intact drug was ≥90% and color and clearness remained unchanged. After 24 h of storage at a controlled temperature, ampicillin solution in 0.9% sodium chloride was found to be stable for 30 h at 25 and 30°C and for 24 h at 37°C. In the ampicillin plus ceftriaxone combined solution, both antibiotics were found to be stable after 30 h of storage at 25 and 30°C, but at 37°C, the stability criterion was not met at any time point. Our study offers solid evidence demonstrating that the concentrations of both drugs at two of the tested temperatures (25°C and 30°C) were stable for up to 30 h. Therefore, both ampicillin alone and ampicillin plus ceftriaxone solutions would be appropriate candidates for inclusion in OPAT programs.

KEYWORDS ampicillin, ceftriaxone, outpatient parenteral antimicrobial therapy, stability, *Enterococcus faecalis*, infective endocarditis

Outpatient parenteral antimicrobial therapy (OPAT) embraces the administration of at least two doses of parenteral antimicrobials on different days without overnight hospital stay (1). OPAT development started in the 1970s and has been widely implemented. The major benefits of OPAT reside in the reduction or avoidance of hospital stays, the reduction of nosocomial infections and hospital-related conditions, significant cost savings, and an improved quality of life for the patient (1, 2). Antimicrobial selection and drug delivery are key elements of OPAT programs. The inclusion of a particular antimicrobial requires the fulfilment of some characteristics, which include appropriateness for a concrete OPAT setting, a suitable dose scheme, simple administration, a manageable toxicity profile, and enough drug stability at room temperature (3).

Ampicillin is a semisynthetic β-lactam antibiotic derived from penicillin. Ampicillin has been employed as a first-line treatment of several infectious diseases, including

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life-threatening infections such as bacteremia, meningitis, or endocarditis (4). The pharmacodynamic parameter best related with β-lactam antibiotic activity is the time above the MIC (T>MIC); therefore, sustained plasma concentrations are extensively required. Despite most β-lactam antibiotics exhibiting half-lives long enough to avoid continuous or recurrent infusion, ampicillin's half-life is notably shorter and entails multiple and frequent administration (5, 6).

Ampicillin plus ceftriaxone combined therapy has been widely recommended for the treatment of *Enterococcus faecalis* infective endocarditis (7, 8). Enterococcal endocarditis treatment routinely enforces 4 to 6 weeks of therapy. After 10 to 15 days, most patients are clinically stable, and antibiotic administration is the only reason to keep them hospitalized (7). Consequently, hospital discharge and treatment continuation through OPAT is a valuable option. During hospitalization, ampicillin and ceftriaxone are administered at 2 g every 4 h and 2 g every 12 h, respectively. Adaptation of this treatment to OPAT ought to avoid the use of two simultaneous electronic pumps on behalf of the patient well-being. The most common approach is the administration of ceftriaxone in a once-daily dose and a administration of a prepared ampicillin daily dose in a single solution every 4 h through a multidose electronic infusion pump (9). Another strategy could be the preparation of daily doses of both antibiotics dissolved in the same solution and also administered through a single electronic pump. In both cases, stability data for solutions administered through pumps are required.

Ampicillin stability in isotonic solutions has been thoroughly studied and discussed (10–13), but differences in study designs warrant further investigation. In contrast, ampicillin plus ceftriaxone combined solution has only been studied by simulation of Y-site administration using glass test tubes over 4 h, with uncertain results (14).

The aim of this study is to evaluate the stability of ampicillin and ampicillin plus ceftriaxone combined in 0.9% sodium chloride solution at three different temperatures in the concentrations proposed for its use in OPAT programs for the treatment of *E. faecalis* infective endocarditis.

RESULTS

Ampicillin 24 g/liter solution stability. After 24 h of storage at controlled temperature, ampicillin solution in 0.9% sodium chloride attained the stability criterion of >90% of the original concentration at 25, 30, and 37°C. However, after 30 h of storage, stability of the solution storage at 37°C decreased and fell below 90% (88.95% ± 4.22%), whereas at 30 and 25°C, it remained stable (101.11% ± 2.19% and 96.43% ± 2.71%, respectively). All ampicillin concentrations dropped below 90% after 48 h of storage, regardless of the storage's temperature. Throughout sampling, solutions were clear and colorless. Ampicillin solution stability data are depicted in Fig. 1.

Ampicillin 24 g/liter plus ceftriaxone 8 g/liter solution stability. Ampicillin stability in a combined solution with ceftriaxone in 0.9% sodium chloride varied from that obtained with ampicillin alone. Drug stability at 25 and 30°C demonstrated a similar profile to that of ampicillin alone, where >90% of the original concentration remained after 30 h of storage. Nevertheless, at 37°C, ampicillin concentration fell to below 90% of the original concentration within the first 20 h. Regarding ceftriaxone stability in a combined solution with ampicillin, after 30 h of storage at 25°C and 48 h of storage at 30°C, the solutions attained the stability criterion of 90% of the original concentration. At 37°C, the concentration decreased to 81.96% ± 1.00% within the first 20 h. No changes in color or clearness were observed. Ampicillin plus ceftriaxone solution stability data are depicted in Fig. 1.

DISCUSSION

International consensus recommends that antimicrobial selection for patient inclusion in OPAT programs should be in concordance with local antimicrobial policy (2, 15, 16). Advances regarding infusion device technology and antimicrobial administration have facilitated a wide inclusion of antimicrobials in OPAT programs (1). These improvements allow following antimicrobial stewardship programs in OPAT antimicrobial

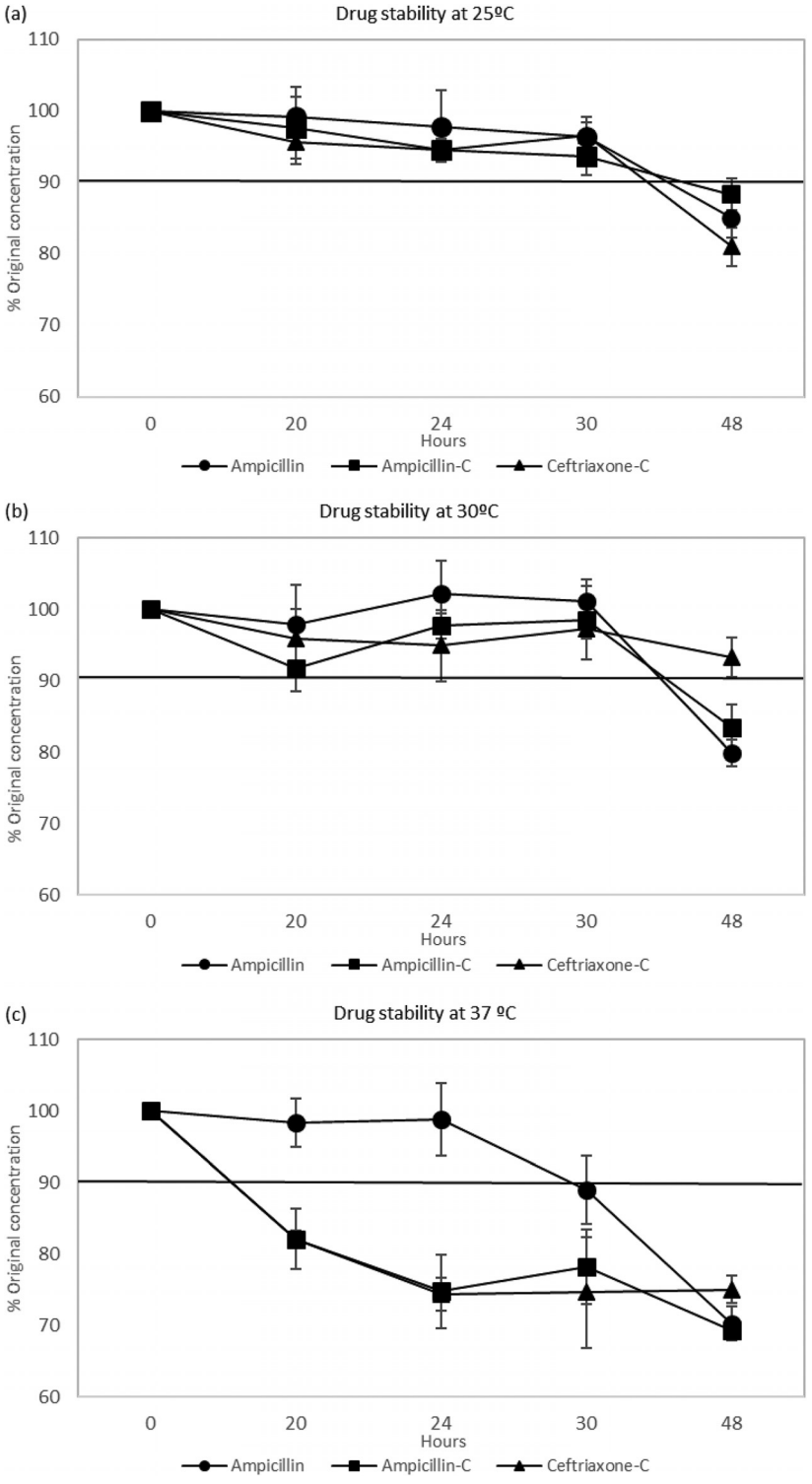

FIG 1 Stability expressed as mean percentage of original concentration with standard error over time at 25°C (a), 30°C (b), and 37°C (c). Ampicillin alone in solution (ampicillin) is represented by a dot. Ampicillin in the combined solution (ampicillin-C) is represented by a square. Ceftriaxone (ceftriaxone-C) in the combined solution is represented by a triangle.

selection. Nevertheless, antimicrobial solution stability still poses a barrier for OPAT administration of some antimicrobial, such as meropenem or ampicillin (1, 16).

Variability in antimicrobial stability studies concerning technique sensitivity, drug concentration, solvent, and container material could hinder drug application in clinical

practice. Over the last 2 decades, some studies concerning ampicillin stability in normal saline have been carried out with significant disparities. Overall, the most commonly used technique was high-performance liquid chromatography (HPLC) coupled to a UV detector (10, 11, 13, 17, 18), but HPLC coupled to a diode array detector (12) and bioassay techniques were also employed (10).

Two conditions that influence ampicillin stability are pH and the solvent nature. A decrease in ampicillin stability has been reported when the solvent increases dextrose concentration, and hence 0.9% sodium chloride is the most common solvent used (13). Maximum ampicillin stability has been described at pH 7.5, while variations to a more acid or basic pH enhance the ampicillin lost (12, 13, 19, 20). Also, temperature and concentration are two factors that commonly influence antimicrobial solution stability, and these are likewise key factors regarding ampicillin stability (12, 13, 21, 22). Another factor that should be considered is the storage container, due to the possibility of drug absorption.

The stability of highly concentrated ampicillin solutions in elastomeric devices has been studied by Nakamura et al. (13) and Kang et al. (11) at 50 g/liter and 30 g/liter, respectively. The first solution was found to be unstable at 25 and 31.1°C, possibly due to its high concentration. On the other hand, ampicillin 30 g/liter solution preserved >90% of the initial concentration after 3 days stored at 25°C. In addition, ampicillin stability at low concentrations has been investigated in different plastic containers (12, 17, 18). In these studies, 12 g/liter and 10 g/liter ampicillin solutions were found to be stable for 24 h at 25°C and 23°C, respectively. Also, Müller et al. (18) tested ampicillin 5 g/liter stability at room temperature, which sustained >90% of the initial concentration for the study period (8 h). Lastly, Juste et al. (10) studied ampicillin stability at 24 g/liter using chromatographic and bioassay techniques. Data obtained from chromatographic methods, which are more sensitive and reliable, showed that ampicillin solution was stable for 24 h. Nonetheless, in-depth information about storage temperature and container material was not detailed in this study.

Regarding ceftriaxone stability, several studies have shown the impact of pH, solvent nature, temperature, and initial concentration on ceftriaxone solutions stability (21, 23–25). As a recent example, Walker et al. (21) studied ceftriaxone stability at 5 and 40 mg/ml in 0.9% sodium chloride and 5% dextrose solution storage at 4 and 23°C. In this study, initial concentration and temperature were the main factors affecting ceftriaxone stability. Nevertheless, the compatibility of ampicillin plus ceftriaxone in solution had been only investigated by one visual study (14). The mixture with other drugs, as well as the impurities and additives of each formulation, could significantly alter ceftriaxone solution stability (26, 27).

In our current work, we studied the stability of ampicillin solutions in analogous conditions to those candidates for the treatment of *E. faecalis* infective endocarditis in OPAT (9, 28). Moreover, ampicillin utility in OPAT is applicable to other infections, such as bacteremia caused by susceptible *Escherichia coli* or enterococcal species or *Listeria monocytogenes* meningitis, providing a secure and low-ecological-impact alternative. Although temperatures higher than 25°C are easily achievable during OPAT administration (29), unaccountably, drug stability at these temperatures is rarely tested, which could have a serious impact on the dose administered during the treatment of life-threatening infections and therefore on the clinical outcome. In this regard, we included a range of temperatures similar to those achievable due to real-life temperature variations inside a room or inside devices in contact with the body (29). For this purpose, we employed HPLC coupled to tandem mass spectrometry (MS/MS) in all of our measurements, which, compared to bioassays and other detectors attachable to liquid chromatography, provides more sensitive and specific results (30). In our study, ampicillin 24 g/liter solution in polypropylene infusion bags attained the stability criterion during 30 h at 25 and 30°C storage temperature. Jointly, we provided unprecedented stability information regarding ampicillin 24 g/liter plus ceftriaxone 8 g/liter combined solution in a polypropylene infusion bag. Both antibiotics preserved >90% of the initial concentration after 30 h of storage at 25 and 30°C.

Our study has several limitations. First, pH changes have not been measured during

assay; nevertheless, the importance of pH lies in its influence in ampicillin degradation, and since ampicillin concentration has been measured, pH control has been omitted. Second, impurities differ among generic brands of ampicillin and ceftriaxone, which could influence drug stability and reduce the extensibility of these results (12, 26, 27). In our study, we tested widely used generic brands that are used in our hospital to increase its applicability. Lastly, isomerization of ceftriaxone under acidic conditions has been reported previously and could affect the antimicrobial activity (31), but our analytical method did not distinguish ceftriaxone isomers.

Conclusion. Our study offers solid evidence demonstrating that the concentrations of both drugs at two of the tested temperatures (25 and 30°C) were stable for up to 30 h. Therefore, both ampicillin alone and ampicillin plus ceftriaxone solutions would be appropriate candidates for inclusion in OPAT programs.

MATERIALS AND METHODS

Materials. Ampicillin sodium and cefixime were purchased from Alsachim (Illkirch, France), and ceftriaxone was obtained as formulations for injection (ceftriaxone sodium for injection; Normon Laboratories). Liquid chromatography-mass spectrometry (LC-MS) grade (reagent grade, >98% pure) acetonitrile was obtained from Merck KGaA (Darmstadt, Germany), and formic acid was obtained from Scharlab (Barcelona, Spain). Ammonium acetate was purchased from Fisher Scientific (NH, USA). Purified water was prepared in-house with a Milli-Q water system from Millipore (Bedford, MA).

Ampicillin and ceftriaxone pharmaceutical dosages were prepared using commercial intravenous formulations (Gobemicina and ceftriaxone sodium for injection; Normon Laboratories). Normal saline (0.9% sodium chloride) polypropylene infusion bags were purchased from Grifols Laboratories (Barcelona, Spain).

Preparation of solutions. Both antibiotics were reconstituted with water for injection (10 ml per g of antibiotic), resulting in a concentration of 100 g/liter. The solutions were further diluted in 0.9% sodium chloride polypropylene infusion bags to obtain the following concentrations: ampicillin 24 g/liter and ceftriaxone 8 g/liter. These concentrations represent the current preparations used for *E. faecalis* infective endocarditis treatment in OPAT (12 g in 0.5 liter and 4 g in 0.5 liter). For each temperature condition, two solutions were prepared that contained ampicillin 24 g/liter and ampicillin 24 g/liter plus ceftriaxone 8 g/liter.

Storage conditions and sample processing. Antibiotic stability was tested at 25°C ± 2°C, 30°C ± 2°C, and 37°C ± 2°C. The solutions were stored in an air thermostat oven for 48 h. Time 0 was defined as the time of antibiotic addition, and 1-ml aliquots were collectedantibiotic addition, and 1-ml aliquots were collected at 0, 20, 24, 30, and 48 h and processed in triplicates. Immediately after collection, samples were diluted 1:10 in Milli-Q water to get a concentration in the range of analysis, vortexed, and aliquoted in autosampler vials. Five microliters of this solutions were injected into the column. Color and clearness were assessed by visual inspection.

HPLC-MS/MS quantification. Samples were analyzed on an Agilent 1290 Infinity liquid chromatograph (Agilent Technologies, Palo Alto, CA) coupled to an AB SCIEX API 4000 mass spectrometer operating in electrospray positive-ionization mode. Monitored transitions were 350.178 → 106.100 (ampicillin), 555.1 → 359.9 (ceftriaxone), and 454.0 → 285.0 (cefixime) *m/z*. Separation was performed on a Phenomenex Luna C18 analytical column (5 μm, 150 × 2.0 mm) with isocratic elution (70/30). The mobile phase consisted of 10 mM ammonium acetate and 1% formic acid (phase A) and acetonitrile and 0.1% formic acid (phase B). Cefixime was used as an internal standard. Ampicillin and ceftriaxone standard curves were highly linear over the ranges of 0.5 to 5 μg/ml ($r = 0.9977$) and 0.25 to 2.5 μg/ml ($r = 0.9979$), respectively. The lower limit of quantification was 0.3 μg/ml for ampicillin and 0.15 μg/ml for ceftriaxone. The accuracy and precision for both antibiotics were <100% ± 15% and <15%, respectively. Validation of the method was performed per FDA guidelines, and the results met the acceptance criteria.

Data analysis. Drug stability was calculated at each sampling time (t) as the percentage (P) of the initial drug concentration (C_o) remaining ($P = C_t / C_0 \times 100$). The concentration of each sample was calculated as the mean of the triplicate assays. The solutions were considered stable if the percentage of intact drug was ≥90% (32). The data are expressed as mean ± standard deviation.

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L.H.-H. wrote the manuscript; L.H.-H. and A.G.-V. designed and conducted the research and analyzed the data; L.H.-H., M.V.G.-N., R.L.-M., L.E.L.-C., J.G.-A., and A.D.A. contributed to the conceptualization; L.F.L.-C. and A.G.-V. provided analytical tools; all authors reviewed and contributed to the final manuscript.

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